What is claimed is:

1. A method for selecting novel binding polypeptides comprising:

(a) constructing a replicable expression vector comprising
a transcription regulatory element operably linked to
a gene fusion encoding a fusion protein wherein the gene fusion comprises
a first gene encoding a polypeptide, and
a second gene encoding at least a portion of a
phage coat protein;

(b) mutating the vector at one or more selected positions within the first gene thereby forming a family of related plasmids;

(c) transforming suitable host cells with the plasmids;

(d) infecting the transformed host cells with a helper phage having a gene encoding the phage coat protein;

(e) culturing the transformed infected host cells under conditions suitable for forming recombinant phagemid particles containing at least a portion of the plasmid and capable of transforming the host, the conditions adjusted so that no more than a minor amount of phagemid particles display more than one copy of the fusion protein on the surface of the particle;

(f) contacting the phagemid particles with a target molecule so that at least a portion of the phagemid particles bind to the target molecule; and

(g) separating the phagemid particles that bind from those that do not.

2. The method of claim 1 further comprising infecting a suitable host cells with the phagemid particles that bind and repeating steps (d) through (g).

3. The method of claim 2 wherein the steps are repeated one or more times.

4. The method of claim 1 wherein the expression vector further comprises a secretory signal sequence.

5. The method of claim 1 wherein the transcription regulatory element is a promoter system selected from the group; *lac* Z, *pho* A, tryptophan, *tac*, λP_L, bacteriophage T7, and combinations thereof.

6. The method of claim 1 wherein the first gene encodes a mammalian protein.

7. The method of claim 6 wherein the protein is selected from the group;
growth hormone, human growth hormone(hGH), des-N-methionyl human growth hormone, bovine growth hormone, parathyroid hormone, thyroxine, insulin A-chain, insulin B-chain, proinsulin, relaxin A-chain, relaxin B-chain, prorelaxin, follicle stimulating hormone(FSH), thyroid stimulating hormone(TSH), leutinizing hormone(LH), glycoprotein hormone receptors, calcitonin, glucagon, factor VIII, an antibody, lung surfactant, urokinase, streptokinase, human tissue-type plasminogen activator (t-PA), bombesin, factor IX, thrombin, hemopoietic growth factor, tumor necrosis factor-alpha and -beta, enkephalinase, human serum albumin, mullerian-inhibiting substance, mouse gonadotropin-associated peptide, β-lactamase, tissue factor protein, inhibin, activin, vascular endothelial growth factor, integrin receptors, thrombopoietin, protein A or D, rheumatoid factors, NGF-β, platelet-growth factor, transforming growth factor ; TGF-alpha and TGF-beta, insulin-like growth factor-I and -II, insulin-like growth factor binding proteins , CD-4, DNase, latency associated peptide, erythropoietin, HER2 ligands, osteoinductive factors, interferon-alpha, -beta, and -gamma, colony stimulating factors (CSFs), M-CSF, GM-CSF, and G-CSF, interleukins (ILs), IL-1, IL-2, IL-3, IL-4, superoxide dismutase; decay accelerating factor, viral antigen, HIV envelope proteins GP120 and GP140, atrial natriuretic peptides A, B, or C, or immuno globulins, and fragments of the above-listed proteins.

8. The method of claim 7 wherein the protein is a human protein.

9. The method of claim 8 wherein the protein comprises more than about 100 amino acid residues.

10. The method of claim 1 wherein the protein comprises a plurality of rigid secondary structures displaying amino acids capable of interacting with the target, and the mutations are primarily produced at positions corresponding to codons encoding the amino acids.

11. The method of claim 10 wherein the rigid secondary structures comprise structures selected from the group; α-(3.6_{13})helix, 3_{10} helix, π-(4.4_{16})helix, parallel and anti-parallel β-pleated sheets, reverse turns, and non-ordered structures.

12. The method of claim 10 wherein the mutations are produced at more than one codon.

13. The method of claim 12 wherein the mutations are produced on more than one rigid secondary structure.

14. The method of claim 1 wherein the helper phage is selected from the group M13KO7, M13R408, M13-VCS, and Phi X 174.

15. The method of claim 14 wherein the helper phage is M13KO7 and the coat protein is the M13 phage gene III coat protein.

16. The method of claim 15 wherein the host is *E. coli*.

17. The method of claim 16 wherein the plasmid is under tight control of the transcription regulatory element.

18. The method of claim 17 wherein the amount is less than about 1%.

19. The method of claim 18 wherein the amount is less than 20% the amount of phagemid particles displaying a single copy of the fusion protein.

20. The method of claim 19 wherein the amount is less than 10%.

21. The method of claim 1 further comprising in step (a), inserting a DNA triplet, encoding an mRNA suppressible terminator codon between said first gene encoding a polypeptide, and said second gene encoding at least a portion of a phage coat protein.

22. The method of claim 21 wherein said mRNA suppressible terminator codon is selected from the following: UAG (amber), UAA (ocher) and UGA (opel).

23. The method of claim 22 wherein said suppressible mutation results in the detectable production of a fusion polypeptide containing sadi polypeptide and said coat protein when said expression vector is grown in a suppressor host cell; and, when grown in a non-suppressor host cell said polypeptide is synthesized substantially without fusion to said phage coat protein.

24. A human growth hormone variant wherein hGH amino acids 172, 174, 176 and 178 respectively are as a group sequentially selected from one of the following: (1)R,S,F,R; (2)R,A,Y,R; (3)K,T,Y,K; (4)R,S,Y,R; (5)K,A,Y,R; (6)R,F,F,R; (7)K,Q,Y,R; (8) R,T,Y,H; (9)Q,R,Y,R; (10)K,K,Y,K; (11)R,S,F,S; and (12)K,S,N,R.

25. A phagemid comprising a replicable expression vector comprising a transcription regulatory element operably linked to a gene fusion encoding a fusion protein wherein the gene fusion comprises a first gene encoding a polypeptide, and a second gene encoding at least a portion of a phage coat protein, wherein a DNA triplet codon encoding an mRNA suppressible terminator codon selected from UAG, UAA and UGA is inserted between the fused ends of the first and second

genes, or is substituted for an amino acid encoding triplet codon adjacent to the gene fusion junction.

26. The phagemid of claim 25 wherein said first gene encodes a mammalian protein.

27. The phagemid of claim 26 wherein the protein is selected from the group: growth hormone, human growth hormone (hGH), des-N-methionyl human growth hormone, bovine growth hormone, parathyroid hormone, thyroxine, insulin A-chain, insulin B-chain, proinsulin, relaxin A-chain, relaxin B-chain, prorelaxin, follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), leutinizing hormone (LH), glycoprotein hormone receptors, calcitonin, glucagon, factor VIII, an antibody, lung surfactant, urokinase, streptokinase, human tissue-type plasminogen activator (t-PA), bombesin, factor IX, thrombin, hemopoietic growth factor, tumor necrosis factor-alpha and-beta, enkephalinase, human serum albumin, mullerian-inhibiting substance, mouse gonadotropin-associated peptide, β-lactamase, tissue factor protein, inhibin, activin, vascular endothelial growth factor, integrin receptors, thrombopoietin, protein A or D, rheumatoid factors, NGF-β, platelet-growth factor, transforming growth factor; TGF-alpha and TGF-beta, insulin-like growth-I and -II, insulin-like growth factor binding proteins, CD-4, DNase, latency associated peptide, erythropoietin, osteoinductive factors, interferon-alpha, -beta, and -gamma, colony stimulating factors (CSFs), M-CSF, GM-CSF, and G-CSF, interleukins (ILs), IL-1, IL-2, IL-3, IL-4, superoxide dismutase; decay accelerating factor, viral antigen, HIV envelope proteins GP120 and GP140, atrial natriuretic peptides A, B or C immuno globulins, and fragments of the above-listed proteins.

28. The phagemid of claim 27 wherein said protein is a human protein.

29. The phagemid of claim 28 wherein the protein comprises more than about 100 amino acid residues.

30. The phagemid of claim 25 wherein said protein comprises a plurality of rigid secondary structures displaying amino acids capable of interacting with the target.

31. The phagemid of claim 30 wherein said rigid secondary structures comprises structures selected from the group; α-(3.6_{13})helix, 3_{10} helix, π-(4.4_{16})helix, parallel and anti-parallel β-pleated sheets, reverse turns, and non-ordered structures.

32. The phagemid of claim 25 wherein the helper phage is selected from the group M13KO7, M13R408, M13-VCS, and Phi X 174.

33. The phagemid of claim 32 wherein the helper phage is M13KO7 and the coat protein is the M13 phage gene III coat protein.

34. The phagemid of claim 33 wherein the host is the *E. coli* wild type or suppressor type.

35. The phagemid of claim 34 wherein the plasmid is under tight control of the transcription regulatory element.

36. The phagemid of claim 35 wherein the number of phagemid particles displaying more than one copy of the fusion protein on the surface of the particles is less than 1%.

37. The phagemid of claim 36 wherein said number of phagemid particles is less than about 10%.

38. The phagemid of claim 37 wherein the number of phagemid particles is less than about 20%.

39. A human growth variant wherein hGH amino acids 10, 14, 18, and 21 respectively are as a group sequentially selected from one of the following:
(1)H,G,N,N; (2)A,W,D,N; (3)F,S,R,L; (4)Y,T,V,N and (5)I,N,I,N.

40. A human growth variant wherein hGH amino acids 174 is serine and 176 is tyrosine and hGH amino acids 167, 171, 175 and 179 respectively are as a group sequentially selected from one of the following:
(1)N,S,T,T; (2)E,S,T,I; (3)K,S,T,L; (4)N,N,T,T; (5) R,D,I,I; and (6)N,S,T,Q.

41. A method for selecting novel binding polypeptides comprising

(a) constructing a replicable expression vector comprising a transcription regulatory element operably linked to DNA encoding a protein of interest containing one or more subunits, wherein the DNA encoding at least one of the subunits is fused to the DNA encoding at least a portion of a phage coat protein;

(b) mutating the DNA encoding the protein of interest at one or more selected positions thereby forming a family of related vectors;

(c) transforming suitable host cells with the vectors;

(d) infecting the transformed host cells with a helper phage having a gene encoding the phage coat protein;

(e) culturing the transformed infected host cells under conditions suitable for forming recombinant phagemid particles containing at least a portion of the plasmid and capable of transforming the host, the conditions adjusted so that no more than a

minor amount of phagemid particles display more than one copy of the fusion protein on the surface of the particle;

(f) contacting the phagemid particles with a target molecule so that at least a portion of the phagemid particles bind to the target molecule; and

(g) separating the phagemid particles that bind from those that do not.

42. The method of claim 41 wherein the expression vector further comprises a secretory signal sequence operably linked to the DNA encoding each subunit of the protein of interest.

43. The method of claim 42 wherein the protein of interest is a mammalian protein.

44. The method of claim 43 wherein the protein of interest is selected from the group; insulin, relaxin, follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), leutinizing hormone (LH), glycoprotein hormone receptors, monoclonal and polyclonal antibodies, lung surfactant, integrin receptors, insulin-like growth factor-I and -II, and fragments of the above-listed proteins.

45. The method of claim 44 wherein the protein of interest is a humanized antibody.

46. The method of claim 45 wherein the protein of interest is a humanized Fab fragment capable of binding to the HER-2 receptor (human epidermal growth factor receptor-2).

47 A human growth hormone (hGH) variant wherein hGH amino acid glutamate$_{174}$ is replaced by serine$_{174}$ and phenylalanine$_{176}$ is replaced by tyrosine$_{176}$ and one or more of the eight naturally occurring hGH amino acids F10, M14, H18, H21, R167, D171, T175 and I179 are replaced by another natural amino acid.

48 The hGH variant of claim 47 wherein the eight naturally occurring hGH amino acids F10, M14, H18, H21, R167, D171, T175 and I179 respectively are as a group replaced with a corresponding amino acid sequentially selected from one of the following groups:

(1) H, G, N, N, N, S, T, T;		(2) H, G, N, N, E, S, T, I;	
(3) H, G, N, N, N, N, T, T;		(4) A, W, D, N, N, S, T, T;	
(5) A, W, D, N, E, S, T, I;		(6) A, W, D, N, N, N, T, T;	
(7) F, S, F, L, N, S, T, T;		(8) F, S, F, L, E, S, T, I;	
(9) F, S, F, L, N, N, T, T.		(10) H, G, N, N, N, S, T, N;	
(11) A, N, D, A, N, N, T, N;		(12) F, S, F, G, H, S, T, T;	
(13) H, Q, T, S, A, D, N, S;		(14) H, G, N, N, N, A, T, T;	
(15) F, S, F, L, S, D, T, T;		(16) A, S, T, N, R, D, T, I;	
(17) Q, Y, N, N, H, S, T, T;		(18) W, G, S, S, R, D, T, I;	
(19) F, L, S, S, K, N, T, V;		(20) W, N, N, S, H, S, T, T;	

(21) A, N, A, S, N, S, T, T; (22) P, S, D, N, R, D, T, I;
(23) H, G, N, N, N, N, T, S; (24) F, S, T, G, R, D, T, I;
(25) M, T, S, N, Q, S, T, T; (26) F, S, F, L, T, S, T, S;
(27) A, W, D, N, R, D, T, I; (28) A, W, D, N, H, S, T, N;
(29) M, Q, M, N, N, S, T, T; (30) H, Y, D, H, R, D, T, T;
(31) L, N, S, H, R, D, T, I; (32) L, N, S, H, T, S, T, T;
(33) A, W, D, N, N, A, T, T; (34) F, S, T, G, R, D, T, I;
(35) A, W, D, N, R, D, T, I; (36) I, Q, E, H, N, S, T, T;
(37) F, S, L, A, N, S, T, V; (38) F, S, F, L, K, D, T, T;
(39) M, A, D, N, N, S, T, T; (40) A, W, D, N, S, S, V, T;
(41) H, Q, Y, S, R, D, T, I.

49. The method of claim 48 wherein said human growth hormone variant (11) further contains leucine$_{15}$ replaced by arginine$_{15}$ and lysine$_{168}$ replaced by arginine$_{168}$.

50. The method of claim 48 wherein said human growth hormone variant (40) further contains phenylalanine$_{176}$

51. A method for selecting novel binding polypeptides comprising:

(a) constructing a replicable expression vector comprising
a transcription regulatory element operably linked to
a gene fusion encoding a fusion protein wherein the gene fusion comprises
a first gene encoding a polypeptide operable connedted to a linking amino acid sequence, and
a second gene encoding at least a portion of a phage coat protein;

(b) mutating the vector at one or more selected positions within the amino acid linking sequence of the first gene thereby forming a family of related plasmids;

(c) transforming suitable host cells with the plasmids;

(d) infecting the transformed host cells with a helper phage having a gene encoding the phage coat protein;

(e) culturing the transformed infected host cells under conditions suitable for forming recombinant phagemid particles containing at least a portion of the plasmid and capable of transforming the host, the conditions adjusted so that no more than a minor amount of phagemid particles display more than one copy of the fusion protein on the surface of the particle;

(f) contacting the phagemid particles with a target molecule so that at least a portion of the phagemid particles bind to the target molecule; and

(g) contacting the bound phagemid particles with a protease capable of hydrolysing the linking a aminio acid sequence of at least a portion of the bound phagmid particles, and

(h) isolating the hydrolyzed phagmid particles.

52. The method of claim 51 further comprising infecting suitable host cells with the hydrolyzed phagemid particles and repeating steps (d) through (h).